Review Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2016, Vol. 36(10) 1653–1667

DOI: 10.1177/0271678X16662891
jcbfm.sagepub.com

SAGE

Cerebral blood flow in small vessel disease: A systematic review and meta-analysis

Yulu Shi[1,2], Michael J Thrippleton[1], Stephen D Makin[1,3], Ian Marshall[1], Mirjam I Geerlings[4], Anton JM de Craen[5,†], Mark A van Buchem[6] and Joanna M Wardlaw[1]

Abstract

White matter hyperintensities are frequent on neuroimaging of older people and are a key feature of cerebral small vessel disease. They are commonly attributed to chronic hypoperfusion, although whether low cerebral blood flow is cause or effect is unclear. We systematically reviewed studies that assessed cerebral blood flow in small vessel disease patients, performed meta-analysis and sensitivity analysis of potential confounders. Thirty-eight studies ($n = 4006$) met the inclusion criteria, including four longitudinal and 34 cross-sectional studies. Most cerebral blood flow data were from grey matter. Twenty-four cross-sectional studies ($n = 1161$) were meta-analysed, showing that cerebral blood flow was lower in subjects with more white matter hyperintensity, globally and in most grey and white matter regions (e.g. mean global cerebral blood flow: standardised mean difference −0.71, 95% CI −1.12, −0.30). These cerebral blood flow differences were attenuated by excluding studies in dementia or that lacked age-matching. Four longitudinal studies ($n = 1079$) gave differing results, e.g., more baseline white matter hyperintensity predated falling cerebral blood flow (3.9 years, $n = 575$); cerebral blood flow was low in regions that developed white matter hyperintensity (1.5 years, $n = 40$). Cerebral blood flow is lower in subjects with more white matter hyperintensity cross-sectionally, but evidence for falling cerebral blood flow predating increasing white matter hyperintensity is conflicting. Future studies should be longitudinal, obtain more white matter data, use better age-correction and stratify by clinical diagnosis.

Keywords

Cerebral blood flow, cerebral small vessel disease, white matter hyperintensities, systematic review, meta-analysis

Received 17 May 2016; Revised 7 July 2016; Accepted 8 July 2016

Introduction

White matter hyperintensities (WMHs) are commonly seen on brain magnetic resonance imaging (MRI) in older people and are considered as one of the core neuroimaging findings of cerebral small vessel disease (SVD). They are defined as patchy or confluent hyperintensities on T2-weighted or FLAIR images, without cavitation, in subcortical white or deep grey matter regions.[1] WMHs are associated with increasing age and vascular risk factors such as hypertension and diabetes.[2] Although the aetiology is not completely understood, chronic hypoperfusion is thought to be a key mechanism,[3] perhaps resulting from narrowing of the arteriolar lumena secondary to lipohyalinosis and arteriolosclerosis. Based on this theory, mechanically induced hypoperfusion models, for example, partial

[1]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom
[2]Department of Neurology, Zhongnan Hospital, Wuhan University, Wuhan, China
[3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom
[4]University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands
[5]Department of Gerontology and Geriatrics, Leiden University Medical Centre, Leiden, Netherlands
[6]Department of Radiology, Leiden University Medical Centre, Leiden, Netherlands
[†]Deceased.

Corresponding author:
Joanna M Wardlaw, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh EH16 4SB, United Kingdom.
Email: Joanna.Wardlaw@ed.ac.uk

or complete carotid artery occlusion, are used to create pathology that appears to mimic human SVD. However, no direct association between carotid artery stenosis and lacunar stroke or WMH has been found in human studies.[4]

Additionally, the relationship between cerebral blood flow (CBF) and WMH is not consistent across human studies. In some cross-sectional studies, low CBF was significantly related to more WMHs, whereas in other studies, no such relationship was found.[5,6] These studies had different study designs, sample sizes and locations where low CBF was detected and most studies were cross-sectional. There are few longitudinal studies. Thus it is unclear whether there is causal relationship between low CBF and WMHs in humans, or whether there is region specificity.

We sought to establish if WMH was related to changes in CBF levels, or whether differences in CBF might be related to potential confounders such as age and tissue loss. We systematically reviewed the available longitudinal and cross-sectional studies in humans, performed a meta-analysis of cross-sectional studies to assess the overall effect size of CBF differences by WMH burden in different brain regions, assessed study quality and performed sensitivity analyses on important confounders.

Methods

We performed this review according to guidelines[7] and a pre-specified protocol. We conducted a literature search of MEDLINE and EMBASE from 1946 up to December 2015, using the Ovid Web Gateway. We used exploded headings related to *Small Vessel Disease* and *Cerebral Blood Flow* with the Boolean operator AND [Supplementary methods]. English and non-English literature were sought. Additional records were identified by hand searching from January 1990 to December 2015 of *Stroke* and *Journal of Cerebral Blood Flow & Metabolism*. We also checked references cited in reviews and primary papers.

Eligibility criteria

We sought longitudinal and cross-sectional primary research studies assessing CBF in subjects with cerebral SVD.[8] Studies measuring cerebral blood flow velocity (CBFv) using Doppler ultrasound techniques were also considered eligible. We excluded studies targeting unilateral or bilateral severe carotid stenosis or occlusion, studies in children, animal studies, duplicate publications, conference abstracts and cross-sectional studies from which we could not extract either absolute values of CBF or correlation/regression coefficients.

Data extraction and analysis

We screened all potentially relevant full papers and extracted data using a standardised form. All data were cross-checked by a second reviewer (JMW). From those that met the inclusion criteria, we extracted data on study population characteristics, study design, SVD and CBF measurement techniques and units. We assessed the study quality using a checklist devised on the basis of the Strengthening the Reporting of Observational Studies in Epidemiology statement (www.equator-network.org) and checklist in a previous paper,[9] including factors such as study population and bias controlling (Supplementary Table S1).

For cross-sectional studies which reported means and standard deviations (S.D.s) of CBF, we extracted data on CBF in disease and control groups or according to SVD burden. Means and S.D.s were extracted from text or tables where available, or from graphs where necessary. For cross-sectional studies where only qualitative data for association between CBF and WMH were available, we included the studies in the review but not in the meta-analysis: we noted the statistical methods, coefficients, P values and other covariates included in regression.

For longitudinal studies, we also listed follow-up durations and primary results extracted from the papers, and contacted the authors to request unpublished data on baseline and follow-up CBF and WMH volume.

Data transformation and analysis

All studies reporting means and S.D.s were included for meta-analysis. For studies that divided patients into more than two grades of WMH severity, we combined the means and S.D.s of groups to create a single pair-wise comparison [Supplementary methods]. As most studies measured CBF in several regions of interest (ROIs), such as different grey matter and white matter regions, we conducted subgroup analysis by brain region. Due to various units of CBF being used in different papers, we calculated the standardised mean differences (SMDs) and 95% confidence intervals (CI) for comparisons using a random-effects model. Sensitivity analyses were carried out for subjects with/without dementia and by age matching between study groups, as both strongly influence CBF. Meta-analyses were conducted using the Cochrane Collaboration's Review Manager (Revman Version 5.3). We assessed for heterogeneity by calculating the I^2 statistic and publication bias using a funnel plot.

Results

A total of 2843 publications were initially identified, of which 75 were potentially eligible and were selected for

further review. We ultimately included 38 articles and excluded (Figure 1): conference abstracts (6), those where we were unable to access the full text (6) or that had no analysable data (18), duplicate publications including the same participant population (3) and studies of severe carotid stenosis or occlusion (4). Note that although presence of arterial diseases was an inclusion criterion of Second Manifestations of ARTerial disease-magnetic resonance (SMART-MR) study, carotid arterial stenosis or occlusion was not one of the criteria: here patients with carotid artery stenosis were included, but they only represented a small proportion of participants, thus we included the study[10] in our review. The 38 studies included a total of 4006 participants: 4/38 were longitudinal and 34/38 were cross-sectional.

Some papers are from the same studies: van der Veen et al.[10] and Bisschops et al.[11] from the SMART-MR study; ten Dam et al.[12] and van Es et al.[13] from the Prospective Study of the Elderly at Risk (PROSPER) trial; Vernooij et al.[14] and Claus et al.[15] from the Rotterdam Scan Study. We were careful to count each participant only once in any analysis.

Characteristics of included studies

Cross-sectional studies. Thirty-four cross-sectional studies were included (Table 1). 24/34 were suitable for meta-analysis. 6/24 studies used patients with dementia plus WMH as disease groups. Of these six studies, two included Alzheimer's disease (AD),[16,17] the other four focused on vascular dementia including subcortical vascular dementia,[18] multi-infarct dementia (MID),[19,20] and Binswanger's disease (BD).[5] AD diagnosis used the criteria of the National Institute of Neurological

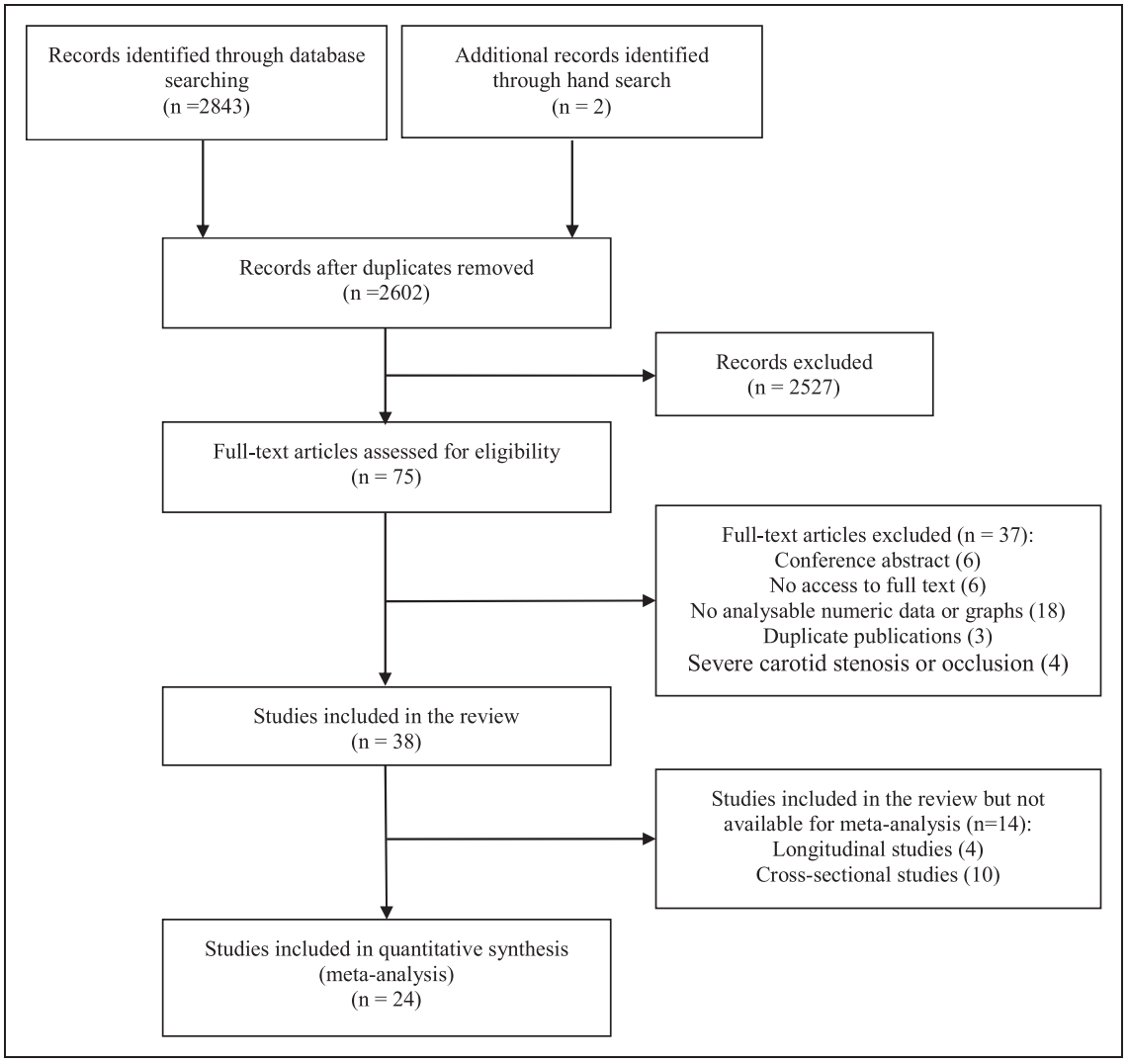

Figure 1. PRISMA flow diagram of literature search.

Table 1. Characteristics of all included studies.

Study	Sample size	Participants	(Baseline) Age (years, mean ± S.D.)	Methods of measuring CBF	CBF units
Longitudinal studies (4)					
Bernbaum et al.[43]	40	High risk TIA or minor ischemic stroke	61.0 ± 11.0	DCS PWI	ml/100 g/min
van der Veen et al.[10]	575	Manifest arterial diseases[a]	57.0 ± 10.0	Phase-contrast MRI	ml/100 ml/min
Kraut et al.[44]	74	Progressive WMH	70.0 ± 6.9	PET	Not shown
		Stable WMH	67.1 ± 7.0		
ten Dam et al.[12]	390	History of vascular disease or were at increased vascular risk	75.0 ± 3.2	Phase-contrast MRI	ml/min
Cross-sectional studies (34)					
Cognitive impairment/dementia (6)					
Kimura et al.[16]	98	Late-onset AD with WMH	78.6 ± 5.1	SPECT	ml/100 g/min
		AD without WMH	77.4 ± 5.0		
Schuff 2009[18]	26	Subcortical vascular dementia	77.0 ± 8.0	ASL	ml/100 g/min
		Cognitively normal	73.0 ± 8.0		
Ibayashi 2000[5]	15	Dementia of BD	60.0 ± 2.0	PET	ml/100 ml/min
		Age-matched hypertensive controls	59.0 ± 2.0		
Yamaji 1997[17]	32	AD with WMH	71.6 ± 3.1	PET	ml/100 ml/min
		AD without WMH	71.0 ± 4.3		
Kawamura et al.[19]	40	MID	64.4 ± 10.2	Xenon CT	ml/100 g/min
		No WMH	67.2 ± 10.5		
Kobari et al.[20]	20	MID	68.1 ± 12.0	Xenon CT	ml/100 g/min
		Neurologically normal controls	52.3 ± 5.7		
No cognitive impairment (18)					
Wagner et al.[45]	36	Extensive WMH	71.0	ASL	ml/100 g/min
		No or mild WMH	67.0		
Fu et al.[33]	56	WMH Grade 3[b]	68.1 ± 8.1	Xenon CT	ml/100 g/min
		WMH Grade 2	68.9 ± 7.7		
		WMH Grade 1	64.5 ± 5.8		
		WMH Grade 0	65.3 ± 6.3		
Nezu et al.[21]	18	Lacunar stroke with severe WMHs	76.0	PET	ml/100 g/min
		Lacunar stroke with mild WMH	74.0		
Huynh et al.[36]	35	TIA with moderate to severe WMH	77.1 ± 6.0	CT perfusion	ml/100 g/min
		TIA with mild WMH	62.6 ± 16.3		
De Bastos-Leite et al.[34]	21	WMH Grade 3[b]	77.7 ± 5.7	ASL	ml/100 ml/min
		WMH Grade 2	74.4 ± 4.6		
		WMH Grade 1	74.0 ± 5.0		
Zheng et al.[22]	35	Asymptomatic WMH	69.7 ± 8.9	SPECT	ml/g/min
		No WMH	67.1 ± 6.9		
Ramli et al.[23]	42	Leukoaraiosis on CT	70.19	CT perfusion	ml/100 g/min
		No leukoaraiosis on CT	69.86		
Kimura et al.[32]	20	Depression (remission) with WMH	78.5 ± 5.1	SPECT	ml/100 g/min
			77.4 ± 5.0		

(continued)

Table 1. Continued

Study	Sample size	Participants	(Baseline) Age (years, mean ± S.D.)	Methods of measuring CBF	CBF units
		Depression (remission) without WMH			
Cui et al.[24]	98	WMH	70.0	TCD, SPECT	cm/s
		No WMH	66.0		
O'Sullivan et al.[25]	36	WMH	68.9 ± 9.2	PET	ml/100 g/min
		No WMH	72.7 ± 7.7		
Yao et al.[26]	10	Extensive WMH	75.0 ± 5.0	Xenon CT	ml/100 g/min
		No WMH	72.0 ± 5.0		
Markus et al.[27]	17	Leukoaraiosis	63.3 ± 12.3	MRI contrast	ml/100 g/min
		No leukoaraiosis	68.3 ± 7.3		
Oishi and Mochizuki[28]	45	WMH	66.8 ± 8.4	Xenon CT	ml/100 g/min
		No WMH	65.1 ± 8.5		
Hatazawa et al.[29]	33	Asymptomatic WMH	71.3 ± 8.6	PET	ml/100 ml/min
		No WMH	68.5 ± 10.2		
Miyazawa et al.[35]	135	WMH Grade IV[c]	71.90 ± 8.17	Xenon CT	ml/100 g/min
		WMH Grade III	69.00 ± 8.08		
		WMH Grade II	67.30 ± 9.87		
		WMH Grade I	64.20 ± 5.55		
		WMH Grade 0	57.3 ± 12.0		
Kuwabara et al.[6]	24	Hypertensive with moderate to severe leukoaraiosis[c]	67.0 ± 9.0	PET	ml/100 ml/min
		Hypertensive with negative to mild leukoaraiosis	54.0 ± 7.0		
		Normotensive control	60.0 ± 12.0		
Kobayashi et al.[30]	246	Apparent PVWMH	67.0 ± 6.1	Xenon CT	ml/100 g/min
		No or mild PVWMH	60.0 ± 8.2		
Fazekas et al.[31]	23	WMH	58.8 ± 5.3	Xenon CT	ml/100 g/min
		No WMH	58.2 ± 2.8		
Studies only showing correlation coefficients (10)					
Crane et al.[47]	26	Mild to severe WMH	73.3 ± 8.8	ASL	ml/100 g/min
Alosco et al.[40]	69	Heart failure with WMH	68.55 ± 8.07	Ultrasound Doppler	cm/s
Heliopoulos et al.[38]	52	Hypertension with WMH	71.4 ± 4.5	Ultrasound Doppler	cm/s
van Es et al.[13]	447	Cerebrovascular risk factors without major neurological deficits	75.0 ± 3.0	Phase-contrast MRI	ml/min, ml/100 ml/min
Vernooij et al.[14]	892	Population-based	67.5 ± 5.5	Phase-contrast MRI	ml/100 g/min
Bisschops et al.[42]	228	Manifest arterial diseases[a]	59.0	Phase-contrast MRI	ml/min
Tzourio et al.[37]	628	Population-based	68.9 ± 2.9	Ultrasound Doppler	m/s
Ott et al.[41]	40	Mixed dementia	72.8 ± 8.7	SPECT	%rCBF relative to cerebellum
Claus et al.[46]	60	Non-demented WMH	65.0–85.0[d]	SPECT	%rCBF relative to cerebellum
Isaka et al.[39]	28	Cerebrovascular risk factors without neurological deficits	67.8	Xenon CT	ml/100 ml/min

S.D.: standard deviation; CBF: cerebral blood flow; TIA: transient ischemic attack; DCS-PWI: dynamic susceptibility contrast perfusion-weighted imaging; MRI: magnetic resonance imaging; AD: Alzheimer's disease; MID: multi-infarct dementia; BD: Binswanger's disease; WMH: white matter hyperintensity; SPECT: single-photon emission computed tomography; ASL: arterial spin labelling MRI; PET: positron emission tomography; TCD: transcranial Doppler; CT: computed tomography; PVWMH: periventricular white matter hyperintensity; rCBF: regional cerebral blood flow. [a]Includes manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm. [b]Fazekas WMH score. [c]Self-designed scoring system for WMH. [d]Age range.

and Communicative Disorders and Stroke, and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) for probable AD. Vascular dementia diagnosis varied: CT/MRI evidence, DSM-III-R criteria,[5,19,20] Hachinski ischaemia scores[19] and the criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centres.[18] In the 18/24 studies of non-demented subjects, 11 compared CBF between subjects having WMHs and normal controls with no or mild WMHs,[21–31] one study performed the comparison between patients with depression (DSM-IV criteria) plus WMHs vs no WMHs,[32] and the other four papers examined the differences in CBF across grades of WMH severity.[6,33–35] Of these four studies, two used Fazekas WMH rating scores,[6,35] the other two used a self-designed rating systems similar to Fazekas's method.[33,34] Two studies recruited patients with acute ischemic symptoms: in Nezu et al.,[21] patients presented with minor ischemic stroke and brain scans were performed at least 3 weeks after onset; Huynh et al. only included TIA patients and brain scans were done acutely.[36]

In the other 10/34 studies which only reported association analysis, two were population-based studies,[14,37] the other nine hospital-based studies included patients with cerebrovascular risk factors,[13,38,39] heart failure,[40] dementia[41] and manifest arterial diseases.[42]

Longitudinal studies. Four longitudinal prospective studies, including 1079 participants, were included (Table 1). Three were hospital-based[10,12,43] and one from a population-based aging study.[44] Among these four studies, Bernbaum et al. recruited participants who presented acute minor stroke symptoms or transient ischemic attack (TIA) and had baseline MRI within 48 h after the onset.[43] The other three studies did not include acute patients. The follow-up durations ranged from 1.5 to 7.7 years. Kraut et al. compared the patterns of long-term CBF change in patients with progressive WMHs to those with stable WMHs,[44] whereas the other three studies performed regression analyses between CBF and WMH data without subdividing patient groups.[10,12,43]

Quality assessment. The average study quality score was 6/9. Scores were mainly lost for not reporting the drop-outs (25/38), no adjustment or matching for risk factors (including age) (17/38), not reporting expertise of image observers (20/38) and not using blinding (25/38) (Supplementary Figure S1).

Assessment of CBF measurement methods. Three studies used phase-contrast MRI,[10,12–14,42] seven used positron emission tomography (PET),[5,6,17,21,25,29,44] six used single-photon emission computerised tomography,[15,16,22,24,32,41] two used MRI contrast,[27,43] two used arterial spin labelling (ASL)-MRI,[18,45] nine used Xenon-CT[19,20,26,28,30,31,33,35,39] and two used CT perfusion[23,36] to assess CBF. Four studies measured CBFv in the middle cerebral arteries using transcranial Doppler ultrasound.[24,37,38,40]

Meta-analysis of differences in CBF by WMH burden

Meta-analysis using SMD in CBF was only possible for 24 cross-sectional studies. Twenty-two brain regions were extracted, but sufficient data were available from only 11 regions which were used by at least three studies and were selected for the primary meta-analysis. These included: global brain mean CBF, basal ganglia, cortical grey matter (total, frontal, temporal, parietal and occipital grey matter) and white matter (total, frontal and occipital white matter, centrum semiovale). Most data were available for grey matter; few studies provided white matter data.

Patients with more severe WMH had lower CBF than patients with mild WMH, globally and in most grey and white matter regions (e.g. mean global CBF: SMD −0.71, 95% CI −1.12, −0.30; total grey matter: SMD −0.50, 95% CI −0.97, −0.03; total white matter: SMD −1.16, 95% CI −1.08, −0.53; see Figure 2a and b), except in basal ganglia (SMD −1.25, 95% CI −2.53, 0.30) and occipital white matter (SMD −0.45, 95% CI −0.96, 0.05) where the difference in CBF did not reach significance. No studies in the meta-analysis separated normal appearing white matter (NAWM) and WMH. However, there was heterogeneity between studies for most of these comparisons (Figure 2a and b) that was not due to publication bias (funnel plot, Supplementary Figure S2). One study found that CBF in patients with lacunar lesions was lower than in those without, however, the result was not adjusted for WMH volume and could not be meta-analysed.[30]

Sensitivity analysis of dementia and age. We repeated the meta-analyses after excluding studies that included patients with dementia and then further excluded studies without age-matching. In most grey and white matter regions, the differences in CBF between subjects with high and low WMH burdens attenuated and were no longer significant, except for mean global brain CBF and centrum semiovale. Most of the trends in the comparisons were still the same, apart from temporal grey matter (Figure 3).

Only one study, Ibayashi et al., used hypertensive but neurologically normal patients as the control group, and found lower CBF in patients with Binswanger's dementia compared to the control group;[5] none of the other studies matched or adjusted

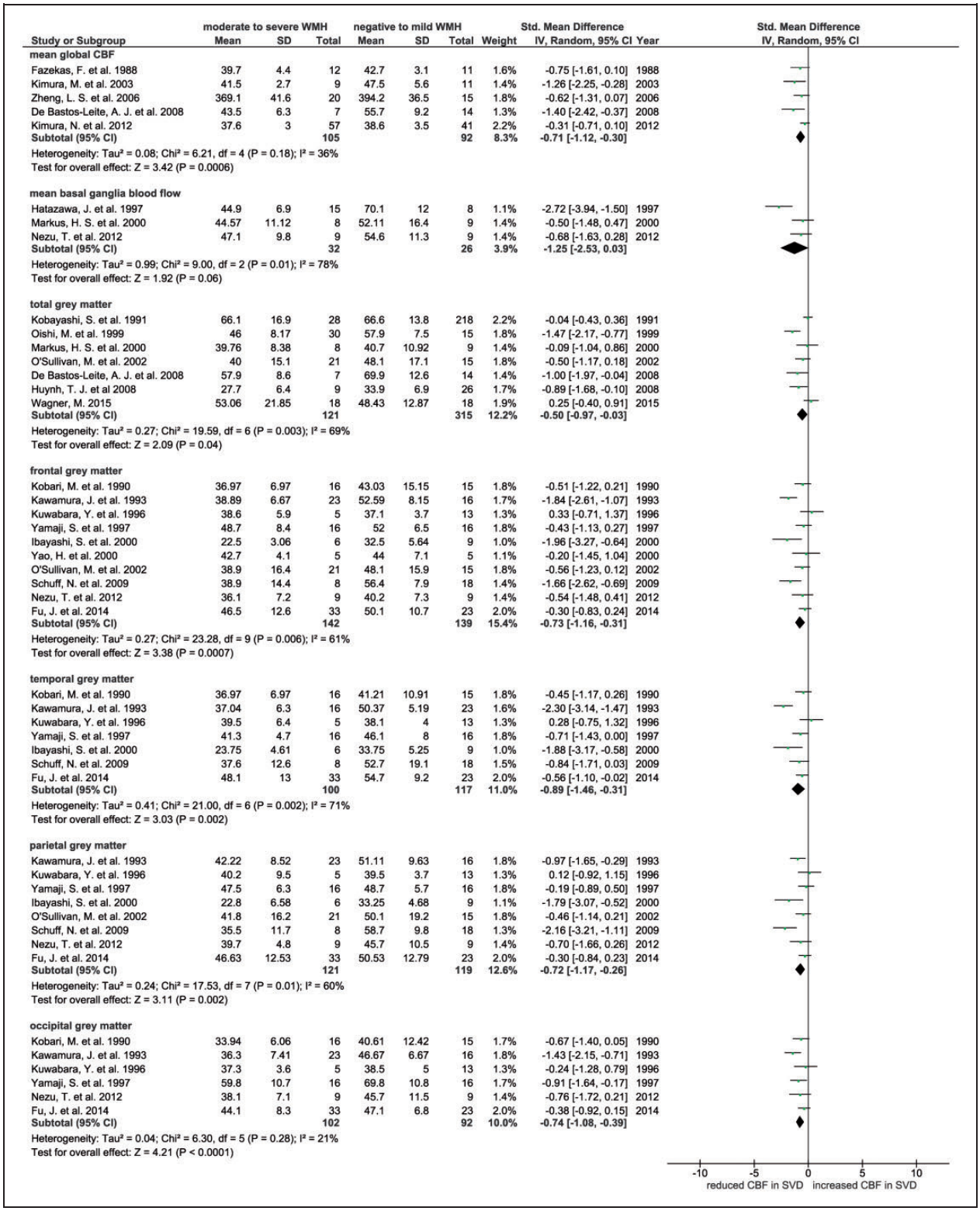

Figure 2. (a) Forest plot showing standard mean differences in global and grey matter CBF in patients with WMH in dementia and non-dementia studies. CBF in different brain regions was analysed in subgroups. (b) Forest plot showing standard mean differences in white matter CBF in patients with WMH in dementia and non-dementia studies. CBF in different brain regions was analysed in subgroups. CBF: cerebral blood flow; WMH: white matter hyperintensity.

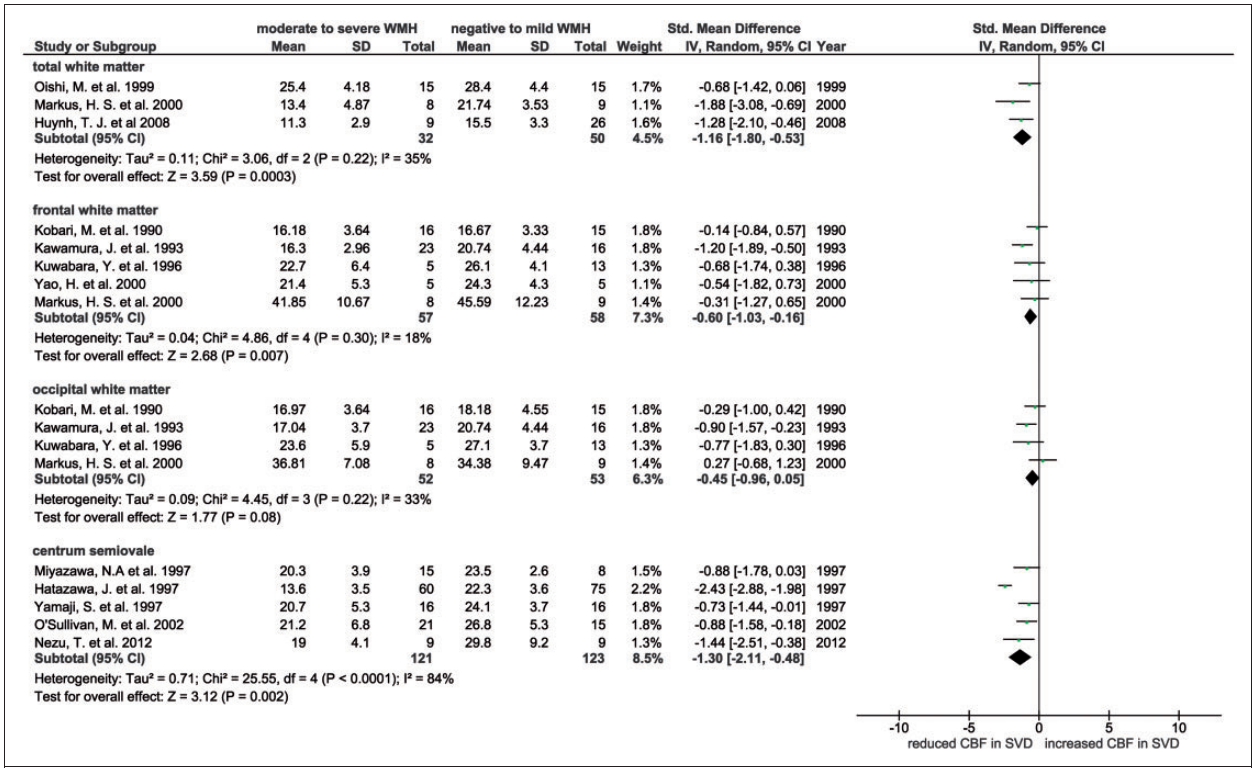

Figure 2. Continued.

for vascular risk factors. Therefore, we were not able to do a sensitivity analysis for vascular risk factors. Hypertension is significantly more prevalent in patients with more severe WMH.

Cross-sectional studies that provided data on associations between CBF and SVD features

Among the 10 cross-sectional papers which only performed association analysis, three studies did not find association between CBF and WMH burden.[39,41,46] Four studies reported that CBF was negatively related to WMH severity.[11,13,14,47] Negative correlation between WMH features and CBFv was found in three studies, of which one assessed CBFv in internal carotid arteries,[38] and the other two in middle cerebral arteries.[37,40] Among all 10 studies, six adjusted for covariates such as age, gender and other vascular risk factors (Table 2).[11,37,40,46–48]

Longitudinal studies

In longitudinal studies, the largest study (575 subjects), van der Veen et al., found that high WMH volume at baseline was significantly associated with falling CBF over 3.9 years follow-up.[10] ten Dam et al. demonstrated in 390 subjects that a decline in global CBF over 2.75 years was associated with a progression in periventricular WMH (PVWMH) but not in deep WMH (DWMH).[12] A small study ($n = 40$) found low CBF in regions that developed WMH over 1.5 years follow-up (Table 3).[43] In contrast to the other findings of falling CBF over time, Kraut et al. demonstrated in 74 subjects that CBF increased in some brain areas (right inferior temporal gyrus, right anterior cingulate and the left superior temporal gyrus) over 7.7 years in patients with progressive WMH.[44] Falling CBF was observed more in the posterior regions including right inferior parietal lobule and right occipital pole but was not specifically associated with WMH change.

Discussion

WMHs are often considered to be a consequence of chronic hypoperfusion. However, while our review of all available published and some unpublished data show that high WMH load is associated with lower CBF, they do not strongly support causation. In cross-sectional studies, low CBF was observed in most of the patients with more WMHs. However the association was damped after removing non-age matched subjects and those with dementia, which suggests that the underlying association is between reduced CBF and age or dementia rather than just WMH. One

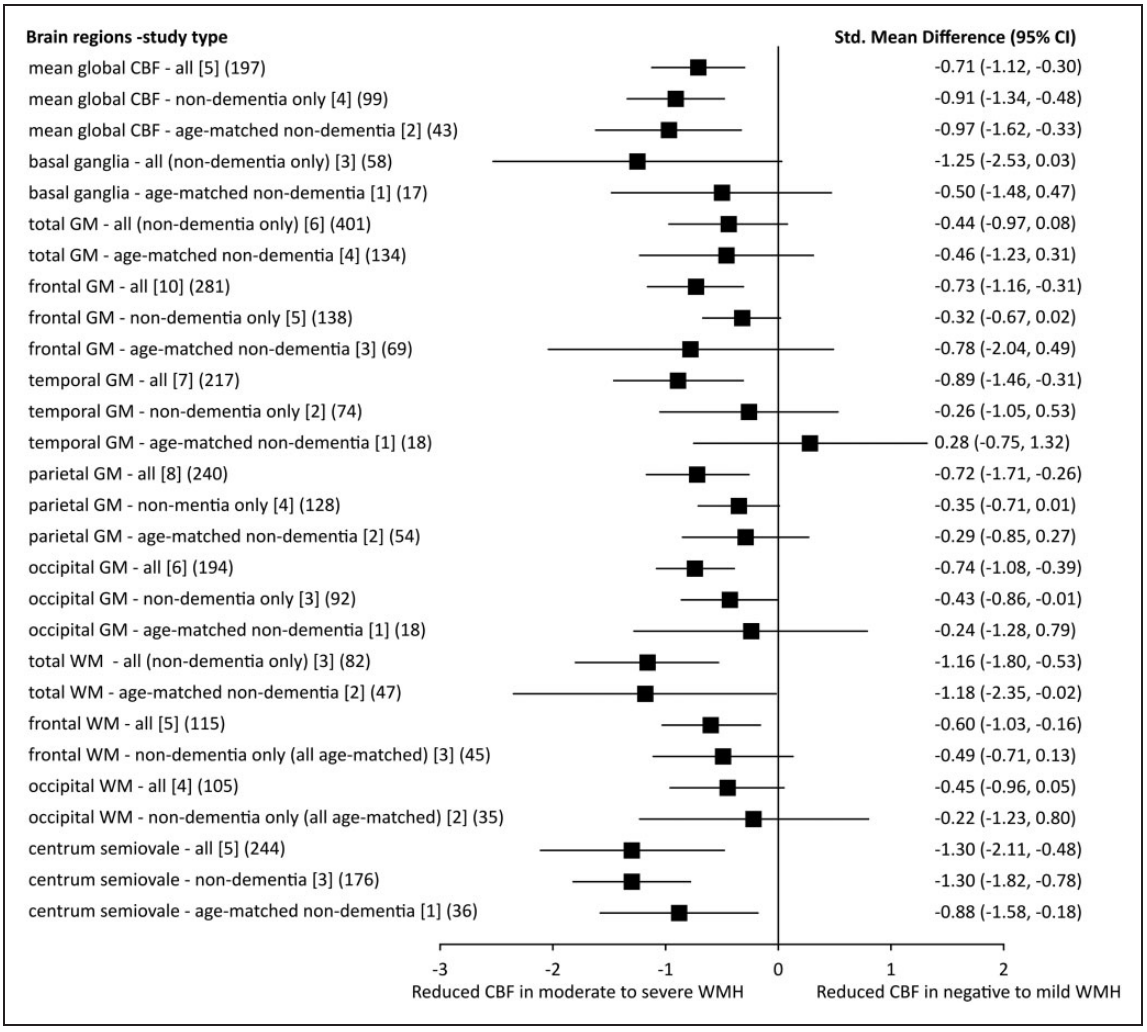

Figure 3. Sensitivity analysis: SMDs of CBF in different brain areas in patients with moderate to severe WMH against those with negative to mild WMH. In each brain area, we showed the SMD of CBF in all studies, after excluding dementia studies and furthermore excluding studies without age-matching [number of studies] (number of participants).
SMD: standard mean difference; CBF: cerebral blood flow; GM: grey matter; WM: white matter; WMH: white matter hyperintensity; CI: confidence interval.

longitudinal study ($n = 575$) also showed a correlation between high baseline WMH volume and decrease in CBF over time, questioning whether a CBF decline causes the tissue loss or vice versa.[10]

The strengths of this systematic review include the use of well-established guidelines for meta-analysis, cautious exclusion of duplicate data, thorough analysis of different study types and sensitivity analysis of clinically important subgroups. Some studies provided more than one comparison but we avoided double-counting the total number of participants. We used every piece of data we could obtain. Studies that recruited subjects with AD, heart failure and depression but compared CBF between patients with and without SVD were also included. Moreover, we included papers in non-English languages, including three papers in Chinese. As most studies measured regional CBF in different brain areas, we carefully chose regions that were mentioned by at least three studies to obtain robust SMDs in meta-analyses.

There are some limitations of the review which in most part reflect the limitation of the literature. First, there are differences between studies in terms of study design and imaging methods which we tried to harmonise to enable comparisons. Longitudinal studies were rare. Data for white matter regions such as centrum semiovale or immediate periventricular white matter were limited or lacking. CBF was obtained by different techniques and varied by technique. However, it is important to note that meta-analysis compares the magnitude of association within one study with that within the others, rather than making direct

Table 2. Results of association-only cross-sectional studies.

Study	Sample size	Statistical method	Results			
			Variables	Coefficients	*P* Values	Adjusted for other variables
Crane et al.[47]	26	Partial correlation (post hoc test)	Mean CBF in cluster (LAP, SC, accumbens, AC and OF) and Fazekas score	Rho = −0.55	0.006	Age, gender
			Mean CBF in cluster (LAI and OF) and Fazekas score	Rho = −0.49	0.015	
			Mean CBF in cluster (LOF and FP) and Fazekas score	Rho = −0.56	0.005	
Alosco et al.[40]	69	Multivariable hierarchical regression	CBFv and WMH volume	$\beta = -0.34$	0.02	Age, gender, premorbid intelligence, depressive symptoms, BMI, hypertension, diabetes, thyroid abnormalities, intracranial volume
Heliopoulos et al.[38]	52	Spearman rank-order correlation	CCA-PSV and WMH score	$r = -0.256$	0.067	No
			CCA-EDV and WMH score	$r = -0.205$	0.144	
			CCA-MFV and WMH score	$r = -0.134$	0.342	
			ICA-PSV and WMH score	$r = -0.135$	0.341	
			ICA-EDV and WMH score	$r = -0.324$	0.019	
			ICA-MFV and WMH score	$r = -0.363$	0.008	
van Es et al.[13]	447	Linear regression model	tCBF and WMH volume	$r = -0.069$	0.148	No
			TCBF and WMH volume	$r = -0.106$	0.044	
Vernooij et al.[14]	892	Linear regression model	WMH volume and tCBF	0.03[a]	NS	Age, gender
			WMH volume and TCBF	0.07[b]	Significant	
Bisschops et al.[42]	282	Linear regression model	WMH score and tCBF	−1.0[c]	0.041	Age, gender, IMT, hypertension
Tzourio et al.[37]	628	Multiple logistic regression	Quartiles of mean CBFv and WMH	OR = 1.4 (1st quartile)	0.22	Age, gender, BMI, hypertension, diabetes, hematocrit, IMT
				OR = 1.6 (2nd quartile)	0.11	
				OR = 2.3 (3rd quartile)	0.006	
Ott et al.[41]	40	Spearman rank-order correlation	Perfusion score and PVWMH score	$r = -0.17$	0.3	No
			Perfusion score and SCWMH score	$r = -0.13$	0.42	
Claus et al.[46]	60	Multiple linear regression model	CBF and grades of severity of WMH	−1.7[d] (Frontal lobe)	NS	Age, gender, type of SPET camera and ventricle-to-brain ratio
				0.4[d] (Parietal lobe)	NS	
				1.2[d] (Temporo-parietal area)	NS	
				−0.4[d] (Temporal lobe)	NS	
Isaka et al.[39]	28	Spearman rank-order correlation	PVWMH score and baseline CBF	$r = -0.364$	NS	No

LAP: left anterior putamen; SC: subcallosal; AC: anterior caudate; OF: orbital frontal; LAI: left anterior insula; LOF: left orbital; FP: frontal pole; CBFv: cerebral blood flow velocity (measured by Ultrasound Doppler); WMH: white matter hyperintensity; BMI: body mass index; CCA: common carotid artery; ICA: internal carotid artery; PSV: peak systolic velocity; EDV: end-diastolic velocity; MFV: mean-flow velocity; tCBF: total cerebral blow flow in ml/min; TCBF: cerebral blood flow per 100 mL brain volume; total brain perfusion: tCBF divided by brain volume; S.D.: standard deviation; lnWMH: natural log transformed white matter hyperintensity volume; IMT: intima media thickness; OR: odds ratio; PVWMH: periventricular white matter hyperintensity; SCWMH: subcortical white matter hyperintensity; NS: not significant; SPET: single-positron emission tomography. [a]Difference in lnWMH volume per S.D. increase in tCBF. [b]Difference in lnWMH volume per S.D. decrease in TCBF. [c]Difference in WMH per 100 ml/min increase in tCBF. [d]Difference in % CBF between persons with no/slight WMH and persons with moderate/severe WMH.

Table 3. Results of longitudinal studies.

		Bernbaum et al.[43]	van der Veen et al.[10]	Kraut et al.[44,a]	ten Dam et al.[12]
Sample size		40	575	74	390
Follow-up time (years)		1.5	3.9	7.7	2.75
CBF	At baseline	16.0 ± 0.2[b] (ml/100 g/min)	52.3 ± 9.8 (ml/100 ml/min)	NA	520.0 ± 88.0 (ml/min)
	At follow-up	NA	NA		504.0 ± 92.0 (ml/min)
WMH (ml)	At baseline	9.21 ± 11.87	2.86 ± 5.44		5.27 ± 9.60
	At follow-up	11.96 ± 13.16	3.74 ± 7.66		7.48 ± 11.70
Association analysis					
bCBF and bWMH volume	Coefficient	NA	NA	NA	TWMH: OR = 1.02 [95%CI: 0.86, 1.21] PVWMH: OR = 1.03 [95%CI: 0.87, 1.21] TWMH: OR = 0.88 [95%CI: 0.74, 1.06]
	P value				NS
bCBF and ΔWMH volume	Coefficient	OR = 0.61 [95%CI: 0.57, 0.65]	PVWMH: B[c] = 0.00 [95%CI: −0.06, 0.05] DWMH: B[c] = 0.04 [95%CI: −0.04, 0.12]		NA
	P value	<0.001	NS		
bWMH volume and ΔCBF	Coefficient	NA	PVWMH: B[d] = −0.61 [95%CI: −1.32, 0.10] DWMH: B[d] = −0.92 [95%CI: −1.56, −0.28]		NA
	P value		PVWMH: NS DWMH: <0.05		
ΔWMH volume and ΔCBF	Coefficient	NA	$r = -0.37$		TWMH: OR = 1.17 [95%CI: 0.84, 1.46] PVWMH: OR = 1.32 [95%CI: 1.06, 1.66] DWMH: OR = 1.00 [95%CI: 0.79, 1.25]
	P value		NS		TWMH: NS PVWMH: 0.015 DWMH: NS
Adjusted for other variables		Age, sex, diabetes, hypertension	Age, sex, follow-up periods, baseline WMHs, cardiovascular risk factors, IMT, carotid stenosis > 50%, non lacunes		Age, sex, baseline atrophy, treatment allocation, baseline CBF

Note: CBF value and WMH volume at both baseline and follow-up, and results of association analysis in longitudinal studies. CBF: cerebral blood flow; WMH: white matter hyperintensity; PVWMH: periventricular white matter hyperintensity; DWMH: deep white matter hyperintensity; TWMH: total white matter hyperintensity; bCBF: baseline CBF; bWMH: baseline white matter hyperintensity; ΔWMH: change of white matter hyperintensity; ΔCBF: change of cerebral blood flow; OR: odds ratio; CI: confidence interval; NA: not available; NS: not significant; IMT: intima media thickness. [a]No numeric data were available from this paper as statistical parametric mapping methods were used as the image analysis tool. [b]CBF of tissues which was normal appearing white matter at baseline but became WMH at follow-up. [c]% change in PVWMH or DWHMs-natural log transformed (% intracranial volume, ICV) per decrease in baseline CBF. [d]Absolute change in CBF per % ICV PVWMH or DWMH (natural log transformed) at baseline.

comparisons of CBF between studies. There are also differences in patient populations: most studies chose patients without neurological symptoms or from community-based populations, whereas three studies recruited patients with acute onset of TIA or minor stroke. Two studies used acute brain MRI as baseline imaging.[36,43] Image analysis methods differed and few if any studies differentiated normal tissue from WMH in the ROIs, thus including more tissue affected by lesions in subjects with high WMH burdens than with few WMH – an obvious confound if measuring CBF. Second, as some studies divided subjects into different severity groups, we converted them into pair-wise comparisons in the form of low WMHs versus high WMHs. Therefore, it is possible that disease groups in the original pair-wise studies might include some patients with mild lesions. Third, the sample sizes of the studies included in meta-analyses were small – the whole analysis of 24 studies included 1161 patients (mean 48/study or 24/group). Only a few studies used age-matched controls. Patients with more severe WMHs were in general significantly older than those who had mild or no WMH, introducing an obvious confound; we addressed this in sensitivity analyses but these were underpowered for meta-regression. In addition, only one study matched for important confounders like vascular risk factors so that sensitivity analysis for risk factors was not possible, and of course hypertension was generally more prevalent in severe WMH groups. Moreover, data for other imaging changes like lacunes or lacunar lesions are lacking.[30]

The meta-analysis demonstrated that CBF measured concurrently was significantly lower in patients with more severe WMH. Cross-sectional studies which only did regression/correlation analyses also showed an association between high WMH burden and low CBF. However, the differences between groups in most brain regions were largely attenuated by excluding dementia and non-age-matched studies, except global mean CBF and CBF in centrum semiovale which remained significant and the point estimate did not move. These results suggest that disease severity and age confound the relationship between WMH and CBF, which was again supported by results from longitudinal studies showing that high burden of WMH predated falling CBF.[10] Additionally, in regression/correlation-only cross-sectional studies where a negative association between WMH and CBF was found, the correlation tends to be significant in more severe patients.[37]

These results indicate that the reduced CBF in patients with WMH might reflect a reduction in the blood supply required by the tissue, due to reduced neuronal activity, or atrophy with fewer cells. As most included studies recorded CBF in cortical grey matter, these associations between reduced CBF and cortical atrophy should not be overlooked. Cortical atrophy is known to occur with the aging process. Results from a large cohort study demonstrated that baseline brain atrophy predicted decline in total CBF over time.[49] There are many imaging studies reporting an association between cortical atrophy and WMH severity.[50] However, there is little information about cortical volume from included studies. Although data for white matter are limited, CBF in frontal and occipital white matter regions changed in the similar way as in grey matter. Results in DWMH and in PVWM differed: a longitudinal study showed that decreasing CBF over time was related to progression of PVWMH rather than to that of DWMH,[12] which is in agreement with a cross-sectional study showing depressed CBF only in NAWM in periventricular regions.[25] The contradictory results from white matter indicate that there might be differential vulnerability for DWMH and PVWMH as these two brain areas are on different sections of the arteriolar tree.[25] However, such a suggestion is not supported by available data – studies indicate that PVWMH and DWMH are on a continuum in terms of location.[51]

The limitation of resting CBF is that it only provides information of a cut-off time point at which CBF might still to be relatively preserved or compensated especially in the early stage of disease.[52] One of the included studies showed a reduced CBF response to hypercapnia in non-demented hypertensive patients with leukoaraiosis while resting CBF was shown to be unaffected.[6] Reduced cerebral vascular reactivity (CVR) represents the dilatory ability of brain vessels, has been suggested as an alternative mechanism of SVD. Risk factors such as hypertension alter the structure of penetrating arterioles by promoting lipohyalinosis and vessel wall thickening, which has led to the suggestion that cerebral arterioles might become stiffer and thus cause a decrease in vasodilatory capacity. Evidences from other studies also suggest that the reduction in CVR might play a critical role in the disease process of SVD.[53] Further studies are required to investigate how blood flow responsiveness (not just resting CBF) varies across different tissues (NAWM, WMHs and grey matter), and how it changes across the course of the disease.

In conclusion, despite large heterogeneities across included studies and the cross-sectional nature of most studies, this systematic review showed that CBF was negatively related to WMH severity. Our results suggest that hypoperfusion in the whole brain and low cortical blood flow is more likely a consequence of WMH than the cause. However, whether WMH is due to focal ischemia in particular white matter tissues and whether development of PVWMHs and DWMHs differs in mechanisms still remain unanswered. This

systematic review emphasises that more data are needed for white matter, especially separate data for NAWM and WMH. Future studies should obtain longitudinal data from white matter as well as grey matter, have larger sample sizes, include appropriate control groups, stratify by and adjust for important cofounders such as age, important risk factors like hypertension, clinical diagnosis (including the type of dementia if relevant), by different features and severities of SVD and by cognitive status. In addition, if studying patients with acute stroke, it would be better to avoid the acute phase after stroke for imaging assessments to avoid effects of the acute stroke interfering with the study of WMH. Moreover, investigation of alternative mechanisms such as impaired CVR and effects of blood–brain barrier changes should be pursued in parallel with CBF measurement to provide new perspectives on treatment for SVD.

Dedication

This paper is dedicated to the memory of Dr Anton J M de Craen who is sorely missed.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Y.S. is funded by China Scholarships Council. M.J.T. is funded by NHS Lothian Research and Development Office. A.J.M.D.C. was and M.A.VB. is an investigator of PROSPER study which was sponsored by an investigator-initiated grant from Bristol Myers-Squibb (Princeton, NJ). J.M.W. was supported by the Scottish Funding Council and Chief Scientist Office through the Scottish Imaging Network A Platform for Scientific Excellence (SINAPSE), the Wellcome Trust funding for SJM and the Medical Research Council through the Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE). The authors hold the data independently of funders.

Acknowledgements

We thank Dr Francesca Chappell and Dr Emily Sena for providing advice on statistical analysis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

S.D.M. and J.M.W. conceived the idea of the study. Y.S. and J.M.W. designed the study. Y.S. did the data search and extracted data and statistical analyses. A.J.M.D.C. (now deceased), M.A.VB. and M.I.G. provided unpublished data for two longitudinal studies. J.M.W. cross-checked the data. Y.S. drafted the report and designed the tables and figures. J.M.W., M.J.T., S.M., I.M., A.J.M.D.C., M.A.VB. and M.I.G. revised the report. All authors approved the manuscript. We regret to report the sudden death of A.J.M.D.C. who is sorely missed and to whom this paper is dedicated.

Supplementary material

Supplementary material for this paper can be found at http://jcbfm.sagepub.com/content/by/supplementary-data

References

1. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–838.
2. Jeerakathil T, Wolf PA, Beiser A, et al. Stroke risk profile predicts white matter hyperintensity volume: The Framingham Study. *Stroke* 2004; 35: 1857–1861.
3. Yata K and Tomimoto H. Chronic cerebral hypoperfusion and dementia. *Neurol Clin Neurosci* 2014; 2: 129–134.
4. Potter GM, Doubal FN, Jackson CA, et al. Lack of association of white matter lesions with ipsilateral carotid artery stenosis. *Cerebrovasc Dis* 2012; 33: 378–384.
5. Ibayashi S, Nagao T, Kuwabara Y, et al. Mechanism for decreased cortical oxygen metabolism in patients with leukoaraiosis: Is disconnection the answer? *J Stroke Cerebrovasc Dis* 2000; 9: 22–26.
6. Kuwabara Y, Ichiya Y, Sasaki M, et al. Cerebral blood flow and vascular response to hypercapnia in hypertensive patients with leukoaraiosis. *Ann Nucl Med* 1996; 10: 293–298.
7. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
8. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–838.
9. Bailey EL, Smith C, Sudlow CL, et al. Pathology of lacunar ischemic stroke in humans – A systematic review. *Brain Pathol* 2012; 22: 583–591.
10. van der Veen PH, Muller M, Vincken KL, et al. Longitudinal relationship between cerebral small-vessel disease and cerebral blood flow: The second manifestations of arterial disease-magnetic resonance study. *Stroke* 2015; 46: 1233–1238.
11. Bisschops RHC, Van Der Graaf Y, Mali WPTM, et al. High total cerebral blood flow is associated with a decrease of white matter lesions. *J Neurol* 2004; 251: 1481–1485.
12. ten Dam VH, Van Den Heuvel DMJ, De Craen AJM, et al. Decline in total cerebral blood flow is linked with increase in periventricular but not deep white matter hyperintensities. *Radiology* 2007; 243: 198–203.
13. van Es AC, van der Grond J, ten Dam VH, et al. Associations between total cerebral blood flow and age related changes of the brain. *PLoS One* 2010; 5: e9825.

14. Vernooij MW, van der Lugt A, Ikram MA, et al. Total cerebral blood flow and total brain perfusion in the general population: the Rotterdam Scan Study. *J Cereb Blood Flow Metab* 2008; 28: 412–419.
15. Claus JJ, Breteler MM, Hasan D, et al. Vascular risk factors, atherosclerosis, cerebral white matter lesions and cerebral perfusion in a population-based study. *Eur J Nucl Med* 1996; 23: 675–682.
16. Kimura N, Nakama H, Nakamura K, et al. Effect of white matter lesions on brain perfusion in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2012; 34: 256–261.
17. Yamaji S, Ishii K, Sasaki M, et al. Changes in cerebral blood flow and oxygen metabolism related to magnetic resonance imaging white matter hyperintensities in Alzheimer's disease. *J Nucl Med* 1997; 38: 1471–1474.
18. Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. *Alzheimers Dement* 2009; 5: 454–462.
19. Kawamura J, Meyer JS, Ichijo M, et al. Correlations of leuko-araiosis with cerebral atrophy and perfusion in elderly normal subjects and demented patients. *J Neurol Neurosurg Psychiatry* 1993; 56: 182–187.
20. Kobari M, Meyer JS, Ichijo M, et al. Leukoaraiosis: Correlation of MR and CT findings with blood flow, atrophy, and cognition. *AJNR Am J Neuroradiol* 1990; 11: 273–281.
21. Nezu T, Yokota C, Uehara T, et al. Preserved acetazolamide reactivity in lacunar patients with severe white-matter lesions: 15O-labeled gas and H_2O positron emission tomography studies. *J Cereb Blood Flow Metab* 2012; 32: 844–850.
22. Zheng LS, Xu J and Wang JP. Quantitative evaluation of regional cerebral blood flow in patients with silent Leukoaraiosis [Chinese]. *Chin J Clin Rehabil* 2006; 10: 80–82.
23. Ramli N, Ho KL, Nawawi O, et al. CT perfusion as a useful tool in the evaluation of leuko-araiosis. *Biomed Imag Interv J* 2006; 2: e16.
24. Cui BW, Qi X and Guo HZ. Comparative study on the cerebral hemodynamics changes between Leukoaraiosis and Binswanger disease [Chinese]. *Chin J Clin Rehabil* 2003; 7: 3460–3461.
25. O'Sullivan M, Lythgoe DJ, Pereira AC, et al. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. *Neurology* 2002; 59: 321–326.
26. Yao H, Yuzuriha T, Fukuda K, et al. Cerebral blood flow in nondemented elderly subjects with extensive deep white matter lesions on magnetic resonance imaging. *J Stroke Cerebrovasc Dis* 2000; 9: 172–175.
27. Markus HS, Lythgoe DJ, Ostegaard L, et al. Reduced cerebral blood flow in white matter in ischaemic leukoaraiosis demonstrated using quantitative exogenous contrast based perfusion MRI. *J Neurol Neurosurg Psychiatry* 2000; 69: 48–53.
28. Oishi M and Mochizuki Y. Differences in regional cerebral blood flow in two types of leuko-araiosis. *J Neurol Sci* 1999; 164: 129–133.
29. Hatazawa J, Shimosegawa E, Satoh T, et al. Subcortical hypoperfusion associated with asymptomatic white matter lesions on magnetic resonance imaging. *Stroke* 1997; 28: 1944–1947.
30. Kobayashi S, Okada K and Yamashita K. Incidence of silent lacunar lesion in normal adults and its relation to cerebral blood flow and risk factors. *Stroke* 1991; 22: 1379–1383.
31. Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: Correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke* 1988; 19: 1285–1288.
32. Kimura M, Shimoda K, Mizumura S, et al. Regional cerebral blood flow in vascular depression assessed by 123I-IMP SPECT. *J Nippon Med Sch* 2003; 70: 321–326.
33. Fu J, Tang J, Han J, et al. The reduction of regional cerebral blood flow in normal-appearing white matter is associated with the severity of white matter lesions in elderly: A Xeon-CT study. *PLoS ONE* 2014; 9: e112832.
34. De Bastos-Leite AJ, Kuijer JPA, Rombouts SARB, et al. Cerebral blood flow by using pulsed arterial spin-labeling in elderly subjects with white matter hyperintensities. *AJNR Am J Neuroradiol* 2008; 29: 1296–1301.
35. Miyazawa N, Satoh T, Hashizume K, et al. Xenon contrast CT-CBF measurements in high-intensity foci on T2-weighted MR images in centrum semiovale of asymptomatic individuals. *Stroke* 1997; 28: 984–987.
36. Huynh TJ, Murphy B, Pettersen JA, et al. CT perfusion quantification of small-vessel ischemic severity. *AJNR Am J Neuroradiol* 2008; 29: 1831–1836.
37. Tzourio C, Levy C, Dufouil C, et al. Low cerebral blood flow velocity and risk of white matter hyperintensities. *Ann Neurol* 2001; 49: 411–414.
38. Heliopoulos I, Artemis D, Vadikolias K, et al. Association of ultrasonographic parameters with subclinical white-matter hyperintensities in hypertensive patients. *Cardiovasc Psychiatry Neurol* 2012; 2012: 616572.
39. Isaka Y, Okamoto M, Ashida K, et al. Decreased cerebrovascular dilatory capacity in subjects with asymptomatic periventricular hyperintensities. *Stroke* 1994; 25: 375–381.
40. Alosco ML, Brickman AM, Spitznagel MB, et al. Cerebral perfusion is associated with white matter hyperintensities in older adults with heart failure. *Congest Heart Fail* 2013; 19: E29–E34.
41. Ott BR, Faberman RS, Noto RB, et al. A SPECT imaging study of MRI white matter hyperintensity in patients with degenerative dementia. *Dement Geriatr Cogn Disord* 1997; 8: 348–354.
42. Bisschops RH, van der Graaf Y, Mali WP, et al. High total cerebral blood flow is associated with a decrease of white matter lesions. *J Neurol* 2004; 251: 1481–1485.
43. Bernbaum M, Menon BK, Fick G, et al. Reduced blood flow in normal white matter predicts development of leukoaraiosis. *J Cereb Blood Flow Metab* 2015; 35: 1610–1615.
44. Kraut MA, Beason-Held LL, Elkins WD, et al. The impact of magnetic resonance imaging-detected white matter hyperintensities on longitudinal changes in

regional cerebral blood flow. *J Cereb Blood Flow Metab* 2008; 28: 190–197.
45. Wagner M, Helfrich M, Volz S, et al. Quantitative T2, T2*, and T2′ MR imaging in patients with ischemic leukoaraiosis might detect microstructural changes and cortical hypoxia. *Neuroradiology* 2015; 57: 1023–1030.
46. Claus JJ, Breteler MMB, Hasan D, et al. Vascular risk factors, atherosclerosis, cerebral white matter lesions and cerebral perfusion in a population-based study. *Eur J Nucl Med* 1996; 23: 675–682.
47. Crane DE, Black SE, Ganda A, et al. Grey matter blood flow and volume are reduced in association with white matter hyperintensity lesion burden: A cross-sectional MRI study. *Front Aging Neurosci* 2015; 7: 131.
48. Vernooij MW, Van Der Lugt A, Ikram MA, et al. Total cerebral blood flow and total brain perfusion in the general population: The Rotterdam Scan Study. *J Cereb Blood Flow Metab* 2008; 28: 412–419.
49. Zonneveld HI, Loehrer EA, Hofman A, et al. The bidirectional association between reduced cerebral blood flow and brain atrophy in the general population. *J Cereb Blood Flow Metab* 2015; 35: 1882–1887.
50. Schmidt R, Ropele S, Enzinger C, et al. White matter lesion progression, brain atrophy, and cognitive decline: The Austrian Stroke Prevention Study. *Ann Neurol* 2005; 58: 610–616.
51. Ryu WS, Woo SH, Schellingerhout D, et al. Grading and interpretation of white matter hyperintensities using statistical maps. *Stroke* 2014; 45: 3567–3575.
52. Østergaard L, Engedal TS, Moreton F, et al. Cerebral small vessel disease: Capillary pathways to stroke and cognitive decline. *J Cereb Blood Flow Metab* 2016; 2: 302–325.
53. Liem MK, Lesnik Oberstein SA, Haan J, et al. Cerebrovascular reactivity is a main determinant of white matter hyperintensity progression in CADASIL. *AJNR Am J Neuroradiol* 2009; 30: 1244–1247.